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# Sex differences in left ventricular electrical dyssynchrony and outcomes with cardiac resynchronization therapy



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**BACKGROUND** Women seem to derive more benefit from cardiac resynchronization therapy (CRT) than men, even after accounting for the higher burden of risk factors for nonresponse often observed in men.

**OBJECTIVE** To assess for sex-specific differences in left ventricular (LV) electrical dyssynchrony as a contributing electrophysiological explanation for the greater degree of CRT benefit among women.

**METHODS** We compared the extent of baseline LV electrical dyssynchrony, as measured by the QRS area (QRSa), among men and women with left bundle branch block (LBBB) undergoing CRT at Duke University (n = 492, 35% women) overall and in relation to baseline QRS characteristics using independent sample *t* tests and Pearson correlation coefficients. Cox regression analyses were used to relate sex, QRSa, and QRS characteristics to the risk of cardiac transplantation, LV assist device implant, or death.

**RESULTS** Although the mean QRS duration (QRSd) did not differ by sex, QRSa was greater for women vs men (113.8  $\mu$ Vs vs 98.2  $\mu$ Vs,  $P < .001$ ), owing to differences in the QRSd <150 ms subgroup

(92.3  $\pm$  28.7  $\mu$ Vs vs 67.6  $\pm$  26.2  $\mu$ Vs,  $P < .001$ ). Among those with nonstrict LBBB, mean QRSd was similar but QRSa was significantly greater among women than men (96.0  $\pm$  25.0  $\mu$ Vs vs 63.6  $\pm$  26.2  $\mu$ Vs,  $P < .001$ ). QRSa was similar among men and women with strict LBBB ( $P = .533$ ). Female sex was associated with better long-term outcomes in an unadjusted model (hazard ratio 0.623, confidence interval 0.454–0.857,  $P = .004$ ) but sex no longer predicted outcomes after accounting for differences in QRSa.

**CONCLUSIONS** Our study suggests that sex-specific differences in LV dyssynchrony contribute to greater CRT benefit among women. Standard QRSd and morphology assessments seem to underestimate the extent of LV electrical dyssynchrony among women with LBBB.

**KEYWORDS** Cardiac resynchronization therapy; Left bundle branch block; QRS duration; Sex; Vectorcardiography

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## Introduction

Cardiac resynchronization therapy (CRT) is the cornerstone of treatment for patients with heart failure with reduced ejection fraction and QRS duration (QRSd) prolongation based on its ability to reduce heart failure hospitalization and mortality and improve quality of life among appropriate candidates.<sup>1</sup> Several studies have identified that in clinical trial<sup>2–4</sup> and nontrial settings,<sup>5–7</sup> women generally have

superior outcomes compared with men after CRT implantation. Although this phenomenon may in part be explained by a higher prevalence of non-sex-based risk factors for nonresponse among men (eg, ischemic heart disease, non-left bundle branch block (LBBB), diabetes, atrial arrhythmias), most studies have identified female sex as an independent predictor of favorable outcomes.

QRS characteristics are important indicators of CRT benefit and are required for patient selection. The QRS area (QRSa) is a robust, validated, noninvasive, vectorcardiographically derived measure of left ventricular (LV) electrical dyssynchrony that has demonstrated substantial relevance to CRT candidacy.<sup>8–13</sup> Increased QRSa is a stronger predictor

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## KEY FINDINGS

- Although QRS duration (QRSd) is used to infer left ventricular (LV) electrical dyssynchrony and, thus, cardiac resynchronization therapy (CRT) candidacy in the relevant guidelines without regard to sex, we found that QRSd is a less reliable indicator of LV electrical dyssynchrony in women compared with men with left bundle branch block (particularly with shorter QRSd).
- Although QRSd is a strong independent predictor of survival free of transplant or LV assist device implantation in men, it does not seem to have prognostic value in women; conversely, QRS area (QRSA) predicts outcomes after CRT among both men and women.
- QRSA reduction with CRT pacing was greater among women than men, suggesting that the greater LV electrical dyssynchrony identified by QRSA is reversible by CRT pacing.

of LV activation delay than QRSd or morphology<sup>10</sup> and is a robust predictor of LV reverse remodeling with CRT.<sup>12</sup> Increased QRSA has also been associated with improved likelihood of survival free of heart transplant or LV assist device (LVAD) after CRT,<sup>8,13</sup> independent of QRS morphology and duration. Our group<sup>9</sup> and others<sup>11</sup> demonstrated that an in-treatment decrease in QRSA (ie, CRT-induced reduction in LV electrical dyssynchrony) is associated with significantly improved outcomes. QRSd reflects the time between start of ventricular activation and the conclusion of ventricular depolarization, regardless of which ventricle contains the most activation delay. As such, significant activation delay in the right or left ventricle manifests as a prolonged QRSd. In contrast, QRSA incorporates information regarding directionality, timing, and vector magnitude. Since vector magnitude is dependent on myocardial mass,<sup>14</sup> QRSA is more specific for identifying how much ventricular mass is experiencing activation delay than QRSd.

Current guidelines most strongly recommend CRT for patients with greater QRSd prolongation and LBBB morphology, without specific regard to sex.<sup>1</sup> It is increasingly recognized that there are sex-specific differences in the relationship between QRS characteristics and outcomes after CRT, such that women tend to derive benefit from CRT at shorter QRSd than men.<sup>3,7,15</sup> However, the actual electrophysiologic rationale for these findings remains unclear. Owing to a critical need to better understand the reasons for sex-specific differences in CRT response,<sup>16</sup> we performed a retrospective analysis of CRT patients to assess the relationships between QRS characteristics, noninvasively assessed LV electrical dyssynchrony via QRSA, and outcomes. We hypothesized that the relationship between electrocardiogram (ECG) characteristics and LV electrical dyssynchrony is fundamentally different among women compared with men.

## Methods

### Study population

We performed a retrospective analysis of patients who received a de novo CRT with defibrillator (CRT-D) from April 2006 to September 2015 at Duke University Hospital owing to an underlying LBBB. Patients were first identified using an institutional dataset prepared for submission to the National Cardiovascular Data Registry. Patients were required to have a digital ECG within the 180 days prior to CRT implantation and survive to discharge. If multiple ECGs were available in the allowable pre-CRT time frame we utilized the ECG closest to the procedure date. Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>17</sup> The study was approved by the Duke Institutional Review Board. The Institutional Review Board waived the need for informed consent owing to the retrospective nature of the study. This study complied with the guidelines set forth in the Declaration of Helsinki.

### ECG analyses

Clinically obtained ECGs were reanalyzed in the GE MUSE Cardiology Information System version 8.0.2.10132 with analysis software version 241 (GE Healthcare, Chicago, IL) and exported in XML format. The fiducial points used to measure QRSd were manually over-read by 2 readers (D.J.F. and K.E.). QRS morphology was designated by the same 2 readers, who were blinded to outcomes. LBBB morphology was further divided into strict and nonstrict LBBB using the Strauss criteria.<sup>18</sup> Notably, the Strauss criteria incorporate information on both QRSd and characteristics (eg, notching).

For the current study, vectorcardiographs were derived from the XML files using customized MATLAB software (MathWorks, Inc, Natick, MA) using the Kors matrices.<sup>19</sup> We calculated the QRSA<sup>8,12</sup> using the median complex. The integral under the depolarization curve was calculated for each of the 3 planes (x, y, z) and the 3-dimensional QRSA was calculated as  $(QRSx^2 + QRSy^2 + QRSz^2)^{1/2}$ .<sup>12</sup>

### Endpoints

The study endpoint was a composite of incident LVAD, cardiac transplant, or death. Endpoint occurrence was determined via a May 24, 2017, query of the Duke Enterprise Data Unified Content Explorer, which incorporates data from billing claims, hospital records, and the Social Security Death Index.<sup>20</sup>

### Statistical analyses

Baseline characteristics of the overall study population stratified by sex were described using proportions for categorical variables and means and standard deviations for continuous variables. Differences between groups were tested using the  $\chi^2$  test for categorical variables and independent sample *t* tests for continuous variables. Correlations between QRSd and QRSA were calculated using Pearson correlation

**Table 1** Baseline characteristics of women and men with left bundle branch block undergoing cardiac resynchronization therapy

Characteristic	Women (n = 172)	Men (n = 320)	P value
Age, years	64.0 (12.2)	66.2 (11.0)	.038
QRS duration, ms	157.0 (18.0)	156.3 (22.9)	.726
QRS area, $\mu$ Vs	113.8 (38.3)	98.2 (44.5)	<.001
Ejection fraction, %	23.1 (7.2)	23.7 (6.8)	.301
Atrial fibrillation or flutter, %	16.9	29.1	.003
Diabetes, %	29.7	33.8	.354
Hypertension, %	62.2	76.9	.001
Ischemic heart disease, %	25.0	59.1	<.001
CABG, %	8.1	35.6	<.001
Dialysis, %	2.3	3.1	.611
NYHA class, %			.481
I	2.3	3.1	
II	16.3	17.8	
III	77.9	75.6	
IV	3.5	3.4	
Primary-prevention ICD indication, %	94.2	87.8	.024
ACE, %	55.8	64.2	.068
ARB, %	25.0	19.0	.120
Amiodarone, %	8.7	18.0	.006
Beta-blocker, %	89.5	90.2	.818
Glomerular filtration rate, mL/min/1.73 m <sup>2</sup>	58 (24)	62 (24)	.080

Numbers in parentheses indicate standard deviation.

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CABG = coronary artery bypass grafting, ICD = implantable cardioverter-defibrillator, LBBB = left bundle branch block, NYHA = New York Heart Association.

coefficients. Differences in the strength of correlation were assessed by calculation of a  $z_{\text{obs}}$ . Sex-based differences in regression lines relating QRSd and QRSA were assessed using ANCOVA. For analyses where QRSA was handled as a categorical variable, a threshold value of  $\geq 95$   $\mu$ Vs was used based on prior work demonstrating this threshold was able to discriminate long-term outcome among CRT patients.<sup>8</sup>

The unadjusted long-term association between patient characteristics and time until transplant, LVAD, or death was visually depicted using a Kaplan-Meier plot. The unadjusted and adjusted risks of various patient and ECG characteristics and time until transplant, LVAD, or death were assessed using Cox proportional hazards models, after confirmation that the proportional hazards assumption was not violated. Adjustment variables included age, atrial fibrillation or flutter, ischemic heart disease, ejection fraction, diabetes, NYHA class, and, depending on the analysis, sex and strict vs nonstrict LBBB. Statistical analysis was performed in SPSS version 1.0.0.1327 (IBM, Armonk, NY). A  $P < .05$  and a  $z_{\text{obs}} < -1.96$  or  $> 1.96$  were considered statistically significant.

## Results

A total of 492 patients with LBBB underwent CRT-D implantation at Duke University between 2006 and 2015 and 35.0% (n = 172) were women. Table 1 depicts differences

in baseline characteristics by sex. Women, when compared with men, were slightly older (66.2 vs 64.0 years,  $P = .038$ ) and more likely to have a primary-prevention implantable cardioverter-defibrillator indication (94.2% vs 87.8%,  $P = .024$ ). Women were less likely to have atrial arrhythmias (16.9% vs 29.1%,  $P = .0003$ ), hypertension (62.2% vs 76.9%,  $P = .001$ ), ischemic heart disease (25.0% vs 59.1%,  $P < .001$ ), and prior coronary artery bypass grafting (8.1% vs 35.6%,  $P < .001$ ). Although QRSd was similar in women and men (157.0 ms vs 156.3 ms,  $P = .726$ , respectively), QRSA was greater in women (113.8  $\mu$ Vs vs 98.2  $\mu$ Vs,  $P < .001$ ). Ejection fraction, NYHA class, and cardiovascular drug use were similar for both sexes. Glomerular filtration rates and rates of dialysis dependence were similar between the 2 groups.

## Relationships between sex, QRSd, and LV electrical dyssynchrony

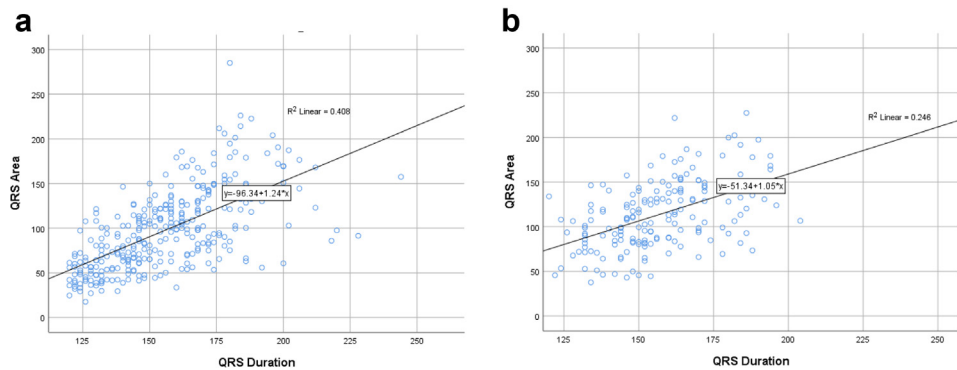
The correlation between QRSd and QRSA was strong among men ( $r = 0.639$ ,  $P < .001$ ) but modest among women ( $r = 0.496$ ,  $P < .001$ ) (Figure 1a and b, respectively); formal testing demonstrated that the strength of correlation was significantly different by sex ( $z_{\text{obs}} = 2.257$ ). Thus, although QRSd was associated with LV electrical dyssynchrony (assessed by QRSA) in both men and women with LBBB, QRSd was a better predictor of LV electrical dyssynchrony in men.

Compared with men, the regression line depicting the relationship between QRSd and QRSA for women demonstrated a less negative y-intercept and a lesser slope (Figure 1). The differences in the regression lines relating QRSd and QRSA by sex were significantly different (ANCOVA  $P < .001$ ). Based on the regression equations, a QRSA of 95  $\mu$ Vs<sup>8</sup> would occur with a QRSd of 154 ms in a man and a QRSd of 139 ms in a woman. Since this relationship could be due to differences in prevalence of strict vs nonstrict LBBB by sex, this analysis was repeated after stratification by strict vs nonstrict LBBB; the relationship between QRSA, QRSd, and sex was the same for both subgroups ( $P = .009$  for sex in strict LBBB cohort,  $P < .001$  for sex in nonstrict LBBB cohort). Among patients with a QRSd of  $< 150$  ms, women had a significantly greater QRSA compared with men ( $92.3 \pm 28.7$   $\mu$ Vs vs  $67.6 \pm 26.2$   $\mu$ Vs,  $P < .001$ ). Among the cohort of patients with a QRSd of  $\geq 150$  ms, women had a slightly greater QRSA that was not statistically significant ( $125.6 \pm 37.9$   $\mu$ Vs vs  $120.6 \pm 41.8$   $\mu$ Vs,  $P = .305$ ). Taken together, this suggests that QRSd systematically underestimates the extent of LV electrical dyssynchrony in women compared with men, particularly at shorter QRSd.

## Relationships between sex, strict vs nonstrict LBBB, and LV electrical dyssynchrony

The overall population was stratified by strict (n = 379) vs nonstrict LBBB (n = 113). Although women with strict LBBB had shorter QRSd than men ( $159.7 \pm 16.7$  ms vs  $166.2 \pm 18.4$ ,  $P < .001$ ), the mean QRSA was similar ( $115.7 \pm 39.1$   $\mu$ Vs for women vs  $113.1 \pm 42.6$   $\mu$ Vs for





**Figure 1** Scatterplots relating QRS duration (x-axis) and QRS area (y-axis) among men (a) and women (b) with superimposed best-fit lines.

men,  $P = .533$ ). Women and men with nonstrict LBBB had similar QRSD ( $132.6 \pm 9.1$  ms vs  $133.2 \pm 13.6$  ms,  $P = .866$ ), but women had significantly greater QRSA compared with men ( $96.0 \pm 25.0$   $\mu$ Vs vs  $63.6 \pm 26.2$   $\mu$ Vs,  $P < .001$ ). Women with nonstrict LBBB were significantly more likely to have a QRSA  $\geq 95$   $\mu$ Vs than men with nonstrict LBBB ( $P < .001$ ; Table 2); among those with strict LBBB, there were no differences by sex ( $P = .894$ ; Table 2).

### QRSD vs QRSA and outcomes

Over a median follow-up of 1110 days (interquartile range 647–2117 days), a total of 201 patients met the primary endpoint (166 patients died, 16 underwent cardiac transplantation, and 19 underwent implantation of an LVAD). In the overall cohort of LBBB patients ( $n = 492$ ), increasing QRSD (hazard ratio [HR] 0.991 per ms, confidence interval [CI] 0.985–0.998,  $P = .007$ ) and QRSA (HR 0.990 per  $\mu$ Vs, CI 0.986–0.993,  $P < .001$ ) were associated with a lower risk of the composite endpoint. In adjusted models including age, sex, ejection fraction, diabetes, atrial fibrillation or flutter, and NYHA class, QRSA (HR 0.991 per  $\mu$ Vs, CI 0.987–0.996,  $P < .001$ ) but not QRSD (HR 0.999 per ms, CI 0.992–1.007,  $P = .888$ ) predicted the composite endpoint.

Female sex was associated with improved outcomes in an unadjusted analysis (HR 0.623, CI 0.454–0.857,  $P = .004$ ) and an adjusted analysis (HR 0.667, CI 0.481–0.925,  $P = .015$ ) accounting for age, ejection fraction, atrial fibrillation or flutter, NYHA class, and QRSD. After additionally adjusting for QRSA in an otherwise similar adjusted model, female sex was no longer associated with outcomes ( $P = .113$ ).

After stratification by sex, QRSD was associated with the composite endpoint in men (HR 0.990 per ms, CI 0.983–0.997,  $P = .004$ ) but not women (HR 0.995 per ms, CI 0.981–1.011,  $P = .553$ ;  $P_{\text{interaction}} = .003$ ). This is graphically illustrated by Kaplan-Meier plots constructed after dichotomizing QRSD using a 150 ms partition (Figure 2). Conversely, QRSA was associated with composite endpoint in both men (0.990 per  $\mu$ Vs, CI 0.986–0.995,  $P < .001$ ) and women (HR 0.990 per  $\mu$ Vs, CI 0.983–0.998,  $P = .011$ ;  $P_{\text{interaction}} < .001$ ). This is graphically illustrated by Kaplan-Meier plots constructed after dichotomizing

QRSA using a 95  $\mu$ Vs partition (Figure 3). In adjusted sex-stratified models, QRSA (but not QRSD) predicted the composite endpoint for women (HR 0.985 per  $\mu$ Vs, CI 0.976–0.995,  $P = .004$ ) and men (HR 0.992 per  $\mu$ Vs, CI 0.987–0.997,  $P = .004$ ).

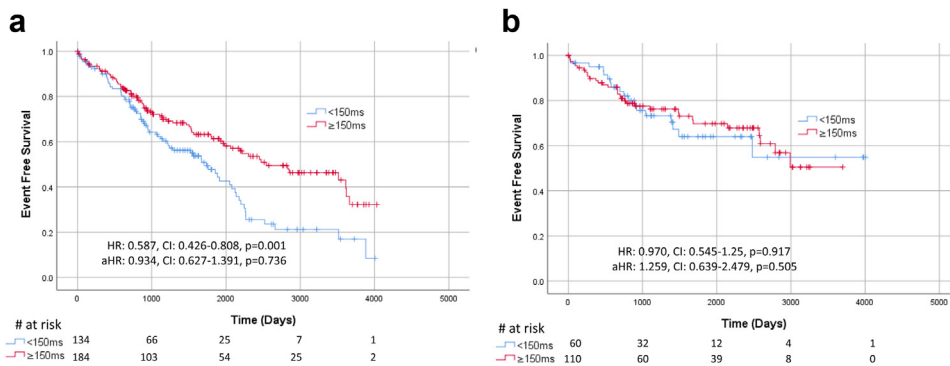
### QRSD in strict vs nonstrict LBBB

Since QRSA is not readily available from current ECG machine vendors, we tested whether the strict vs nonstrict LBBB designation could improve prognostication compared to QRSD. In unadjusted analyses, presence of strict LBBB was associated with a significantly lower risk of the composite endpoint (HR 0.612, CI 0.452–0.827,  $P = .001$ ). There was a significant interaction between sex and strict vs nonstrict LBBB ( $P_{\text{interaction}} = .015$ ) and in unadjusted sex-stratified analyses, strict LBBB was associated with significantly lower risk of the composite endpoint among men (HR 0.692, CI 0.494–0.968,  $P = .031$ ) and trended toward being associated with a lower risk in women (HR 0.539, CI 0.252–1.151,  $P = .110$ ). In adjusted sex-stratified models, strict vs nonstrict LBBB was not associated with outcomes in either sex and QRSD was associated with outcomes in men but not women (HR 0.989 per ms, CI 0.979–1.00,  $P = .041$ ). These results show that use of strict vs nonstrict LBBB does not improve prognostication beyond use of QRSD, particularly in women.

**Table 2** Sex-stratified comparison of the proportion of patients with a QRS area  $\geq 95$   $\mu$ Vs by strict vs nonstrict left bundle branch block

Sex	QRSA $\geq 95$ $\mu$ Vs	Strict LBBB		Nonstrict LBBB		$P$ value
		Count	Column N %	Count	Column N %	
Male	No	78	34.8%	84	87.5%	<.001
	Yes	146	65.2%	12	12.5%	
Female	No	55	35.5%	7	41.2%	.643
	Yes	100	64.5%	10	58.8%	

LBBB = left bundle branch block; QRSA = QRS area.



**Figure 2** Kaplan-Meier plots comparing survival free of left ventricular assist device or cardiac transplant among men (a) and women (b) after stratification by QRS duration with a 150 ms partition. The multivariable model was adjusted for age, ejection fraction, atrial fibrillation or flutter, NYHA class, and QRS area (as a continuous variable).

### CRT-induced changes in QRSa by sex

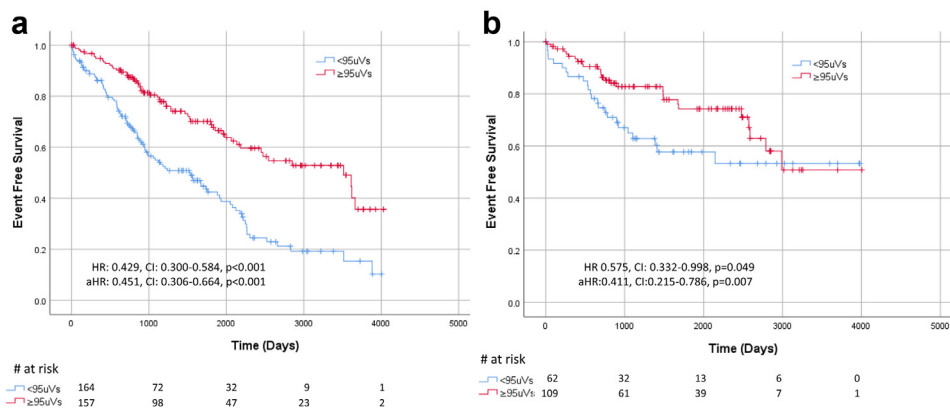
A total of 351 patients (128 female) had paired baseline and follow-up post-CRT ECGs suitable for QRSa assessment. Overall, women had a greater reduction in QRSa with CRT pacing than men ( $-45.5 \pm 41.9 \mu\text{Vs}$  vs  $-31.3 \pm 42.3 \mu\text{Vs}$ ,  $P = .003$ ) and this difference was driven by the subgroup of patients with a QRSd  $<150$  ms ( $-27.6 \pm 40.6 \mu\text{Vs}$  vs  $-10.6 \pm 34.6 \mu\text{Vs}$ ,  $P = .019$ , for women vs men, respectively).

### Discussion

This report, which assessed sex-based differences in QRSd, LV electrical dyssynchrony, and outcomes among patients with LBBB undergoing CRT-D, has several key findings. First, although QRSd is used to infer LV electrical dyssynchrony and, thus, CRT candidacy in the relevant guidelines without regard to sex, we found that QRSd is a less reliable indicator of LV electrical dyssynchrony in women compared with men. Specifically, QRSd systematically underestimates the extent of LV electrical dyssynchrony in women, particularly those with a QRSd  $<150$  ms. Second, although women and men with strict LBBB have overall similar degrees of LV

electrical dyssynchrony, women with nonstrict LBBB have significantly more LV electrical dyssynchrony compared with men with nonstrict LBBB. Third, although QRSd is a robust independent predictor of survival free of transplant or LVAD implantation in men, it does not seem to have prognostic value in women. Fourth, QRSa was a robust predictor of event-free survival in both men and women. Fifth, the use of strict vs nonstrict LBBB does not improve prognostication beyond use of QRSd, particularly in women. Finally, QRSa reduction with CRT pacing was greater among women than men, suggesting that the greater LV electrical dyssynchrony identified by QRSa is reversible by CRT pacing. Taken together, these results identify a key mechanism underpinning the observation that women seem to derive more benefit from CRT compared with men and support the notion that CRT guidelines may eventually need to consider sex-specific criteria.

We found that adding QRSa to a multivariable model rendered sex an insignificant predictor of outcomes after CRT. These findings are consistent with a prior study by Okafor and colleagues.<sup>11</sup> However, our study extended these findings by creating 2 successive models to demonstrate that female sex remained a predictor of outcomes in adjusted



**Figure 3** Kaplan-Meier plots comparing survival free of left ventricular assist device or cardiac transplant among men (a) and women (b) after stratification by QRS area with a 95  $\mu\text{Vs}$  partition. The multivariable model was adjusted for age, ejection fraction, atrial fibrillation or flutter, NYHA class, and QRS duration (as a continuous variable).

models until QRSA was entered into the model. Thus, although the results from our manuscript were concordant with those from Okafor and colleagues, our sequential approach to model building allows one to make firmer conclusions regarding the relationship between sex, QRSA, and outcomes after CRT implantation.

There are several potential explanations for why women have greater LV electrical dyssynchrony relative to men, particularly at shorter QRSd. The QRS complex in LBBB typically begins with depolarization of the right ventricle. The septal LV endocardium is depolarized 40–80 ms after QRS onset via transseptal conduction and the activation wavefront concludes at the lateral LV epicardium at the terminal portion of the QRS.<sup>21</sup> Women may have faster transseptal conduction times than men, and therefore a greater proportion of the QRSd may be composed of LV activation time. If so, QRSd would be expected to be shorter in women than in men, and may systematically underestimate LV activation time in women. Faster transseptal conduction times could be due to differences in the location of block within the left bundle branch in women compared with men<sup>22</sup>; differences in the number and/or location of septal breakthrough sites; differences in septal myocardial conduction velocity; differences in septal fiber orientation, fibrosis, or scarring<sup>23,24</sup>; differences in the presence or distribution of septal fascicles; or differences in septal myocardial thickness.<sup>25</sup> It is also possible that differences in LV size between men and women may influence the observed differences in LV electrical dyssynchrony.

Prior studies have demonstrated that among CRT patients with LBBB, the normalization of QRS for LV size accounts for the sex-specific differences in echocardiographic response<sup>26</sup> and survival free of LVAD, transplant, or death.<sup>27</sup> These studies suggest that women, compared to men, have more electrical dyssynchrony. Our study extends these important findings by directly measuring sex-specific differences in baseline electrical dyssynchrony (defined by QRSA) and CRT-induced decreases in electrical dyssynchrony (defined by change in QRSA). Furthermore, these differences in baseline and in treatment dyssynchrony remained significant after accounting for baseline QRS duration, underscoring the challenges associated with using QRS duration as a measure of electrical dyssynchrony. Mechanisms other than differences in LV size may account for the differences in LV electrical dyssynchrony observed between men and women.

Current CRT guidelines are sex agnostic and use standard 12-lead ECG criteria (QRSd and morphology) to assess the extent of LV electrical dyssynchrony.<sup>1</sup> Among symptomatic heart failure patients with LVEF  $\leq 35\%$  and LBBB, CRT is recommended as a class I indication if QRSd is  $\geq 150$  ms and a class IIa indication if the QRSd is  $< 150$  ms. Results from our study are consistent with many prior studies that have concluded that sex-specific CRT criteria should be considered. Additionally, our study is the first to report that (1) women have more LV electrical dyssynchrony compared with men and (2) QRSd systematically underestimates the

extent of LV electrical dyssynchrony in women, particularly at shorter QRSd. Taken together, these findings support the need for future prospective studies that could inform adoption of sex-specific CRT guidelines. Finally, if automated QRSA assessment becomes widely available, it could prove clinically useful in determining CRT candidacy rather than QRSd, as the former seems more accurate than the latter at identifying LV electrical dyssynchrony (regardless of sex).

In the current era, the most important application of making an ECG diagnosis of LBBB in heart failure patients is to determine CRT candidacy.<sup>18</sup> The nearly decade-old proposal by Strauss and colleagues<sup>18</sup> to modify the definition of LBBB to include sex-specific QRSd criteria ( $\geq 130$  ms in women,  $\geq 140$  ms in men) and evidence for delayed LV activation (ie, notching in consecutive leads) was an important step forward. Results from the current study, which demonstrate significant LV electrical dyssynchrony in women (but not men) with nonstrict LBBB, suggest that the current Strauss criteria may misclassify a significant proportion of “true” LBBB, especially in women. These observations should prompt consideration of new LBBB criteria.

## Limitations

This study has several important limitations, including the retrospective study design and single-center nature. Although we were able to characterize sex-specific differences in LV electrical dyssynchrony, the absence of a control group prevented us from assessing for sex-specific QRSA thresholds for determining CRT benefit. Although QRSA is a strong predictor of LV activation delay,<sup>10</sup> it also incorporates information on the magnitude of the unopposed vectors and should not be considered a direct measure of LV activation delay. No direct measure of LV activation delay was available for this study. Nonfatal endpoints (LVAD and transplant) were obtained from health system billing records and were not adjudicated based on blinded committee assessment. Mode of death was not available. Although our adjusted models included numerous clinical characteristics, we cannot rule out the possibility of residual confounding. The study was conducted at a quaternary care center and therefore the results may not be generalizable to other patient care settings.

## Conclusions

We identified sex-specific differences in LV electrical dyssynchrony that seem to contribute to the greater observed CRT benefit among women. Standard QRSd and morphology assessment underestimates the extent of LV electrical dyssynchrony among women with LBBB, particularly in the context of shorter QRSd. Prospective studies are needed to assess if sex-specific CRT criteria are warranted.

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